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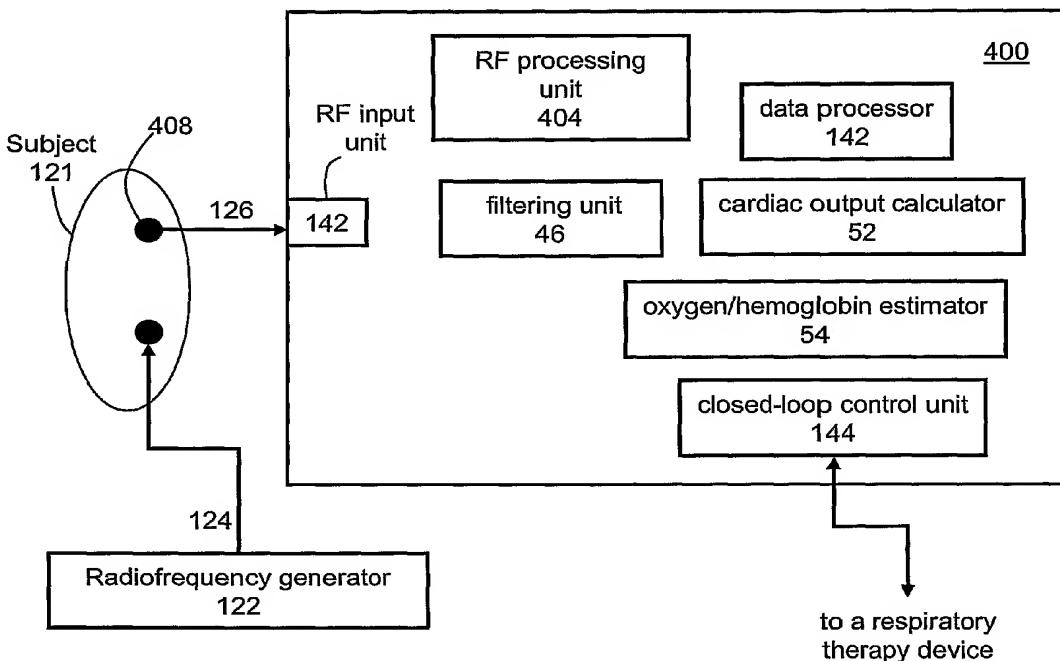
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(54) Title: METHOD AND SYSTEM FOR MONITORING SLEEP



(57) Abstract: A method of monitoring sleep of a sleeping subject is disclosed. The method comprises determining a phase shift of input radiofrequency signals received from the subject during sleep relative to output radiofrequency signals transmitted to the subject during sleep, calculating cardiac output based on the phase shift, and using the cardiac output for identifying sleep apnea events.

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## METHOD AND SYSTEM FOR MONITORING SLEEP

FIELD AND BACKGROUND OF THE INVENTION

The present invention, in some embodiments thereof, relates to medical application and, more particularly, but not exclusively, to a method and system for monitoring sleep.

Apnea is a Greek word meaning "without breath" which is used in the literature to describe a condition of a temporary pause in breathing. Sleep apnea refers to the temporary cessation of breathing during sleep. Sleep apneas have been classified into three types: obstructive sleep apnea (OSA), central sleep apnea (CSA) and mixed sleep apnea (MSA). The difference between obstructive sleep apnea and central sleep apnea is that in obstructive sleep apnea the breathing passageways are blocked, while in central sleep apnea the neural drive to respiratory muscles is transiently abolished but the passageways can still be open. In central sleep apnea the lungs form a reservoir for air flow even though the individual is not breathing.

Mixed sleep apnea consists of a central sleep apnea component and an obstructive sleep apnea component. In mixed sleep apnea, the obstructive component typically follows the central component. The most common type of sleep apnea is obstructive sleep apnea.

Also known are obstructive sleep hypopnea, which is a milder form of obstructive apnea characterized by partial obstruction of the upper airway passages, and central sleep hypopnea, which is a milder form of central sleep apnea characterized by shallow breathing while the upper airway are open.

An apnea event generally leads to a progressive-type asphyxia until the individual is briefly aroused from the sleeping state, thereby restoring airway patency or respiratory muscles activity thereby restoring airflow to the lung. Consequently, sleep of individuals diagnosed with sleep apnea is fragmented and of poor quality.

Sleep apneas, particularly of the obstructive type, are recognized as life-threatening conditions. Individuals with sleep apnea have an increased risk of suffocating during sleep or during surgery requiring general anesthesia.

Sleep apnea is diagnosed using a test called Polysomnography (PSG), which involves the patient sleeping in a sleep lab connected to various measurement

instruments. The test provides an Apnea/Hypopnea Index (AHI) which drives a diagnosis of sleep apnea along with severity.

When an individual is diagnosed with sleep apnea, the individual may be prescribed a therapeutic regime involving the use of a Continuous Positive Airway Pressure (CPAP) device. The CPAP device works by delivering a steady flow of air through a soft, pliable mask worn over the individual's nose. The CPAP device essentially pressurizes the throat of the individual thereby preventing the collapse of the soft tissue and keeping the airways open and allowing the individual to breathe uninterrupted during sleep.

For more severe cases of OSA, surgery such as laser assisted uvuloplasty is used to provide a partial treatment. Additional types of treatments are disclosed in U.S. Patent Nos. 5,988,171, 6,250,307, 6,523,542, 6,431,174 and 6,601,584.

#### SUMMARY OF THE INVENTION

According to an aspect of some embodiments of the present invention there is provided a method of monitoring sleep of a sleeping subject using output radiofrequency signals transmitted to the subject during sleep and input radiofrequency signals received from the subject during sleep. The method comprises determining a phase shift of the input radiofrequency signals relative to the output radiofrequency signals, calculating cardiac output based on the phase shift, and using the cardiac output for identifying sleep apnea events.

According to an aspect of some embodiments of the present invention there is provided a method of monitoring sleep of a sleeping subject. The method comprises transmitting output radiofrequency signals to the subject during sleep, receiving input radiofrequency signals from the subject during sleep, and executing the method described above.

According to some embodiments of the present invention the method further comprises supplementing the cardiac output with blood oxygen content which can be measured, for example, via pulse oximetry. In these embodiments, the identification of the sleep apnea events can be based on the cardiac output and the blood oxygen content. For example, total oxygen delivery can be estimated as further detailed hereinunder.

According to some embodiments of the present invention the method further comprises estimating or receiving hemoglobin concentration of the sleeping subject. In some embodiments, the hemoglobin concentration is used for estimating oxygen content.

5 According to some embodiments of the present invention the method further comprises estimating total oxygen delivery and generating a wakening signal when an estimated value is below a predetermined threshold.

10 According to some embodiments of the invention the identification of the sleep apnea events is further based on the estimated value of the total oxygen delivery.

15 According to some embodiments of the present invention the method further comprises controlling positive airway pressure delivered to the subject based on the estimated value of the total oxygen delivery. In various exemplary embodiments of the invention the control of airway pressure is in a closed loop feedback with the estimation of total oxygen delivery. Thus, the method controls the delivered positive airway pressure such as to ensure that the estimated amount of total oxygen delivery is above a predetermined threshold, or within a predetermined range.

20 According to some embodiments of the present invention the method further comprises reducing or eliminating amplitude modulation of the input radiofrequency signals so as to provide input radiofrequency signals of substantially constant envelope.

25 According to some embodiments of the present invention the method further comprises mixing the output radiofrequency signals and the input radiofrequency signals so as to provide a mixed radiofrequency signal, and filtering out a portion of the mixed radiofrequency signal so as to substantially increase a signal-to-noise ratio of a remaining portion of the mixed radiofrequency signal.

According to some embodiments of the present invention the method further comprises applying a dynamically variable filter.

30 According to an aspect of some embodiments of the present invention there is provided apparatus for monitoring sleep of a sleeping subject using output radiofrequency signals transmitted to the subject during sleep and input radiofrequency signals received from the subject during sleep. The apparatus comprises a phase shift determinator configured for determining a phase shift of the

input radiofrequency signals relative to the output radiofrequency signals, a cardiac output calculator configured for calculating cardiac output based on the phase shift, and a sleep apnea identification unit configured for identifying sleep apnea events based on the cardiac output.

5 According to an aspect of some embodiments of the present invention there is provided a system for monitoring sleep of a sleeping subject. The system comprises a radiofrequency generator for generating output radiofrequency signals, a plurality of electrodes designed for transmitting the output radiofrequency signals to the subject and for sensing input radiofrequency signals from the subject, and the monitoring apparatus described above.

According to some embodiments of the present invention the system further comprises a blood oxygen measuring device, wherein the sleep apnea identification unit is configured to identify the sleep apnea events based on the cardiac output and the blood oxygen content.

15 According to some embodiments of the present invention the apparatus further comprises a total oxygen delivery estimator configured for estimating total oxygen delivery.

According to some embodiments of the invention the sleep apnea identification unit is configured to identify the sleep apnea events based on an estimated value of the total oxygen delivery and the cardiac output.

According to some embodiments of the invention the system comprises a respiratory therapy device, such as, but not limited to, a continuous positive airway pressure (CPAP) device.

According to some embodiments of the invention the apparatus comprises a closed-loop control unit which receives the estimated value of total oxygen delivery from the total oxygen delivery estimator and controls the pressure delivered by the respiratory therapy device based on the estimated value. In various exemplary embodiments of the invention the closed-loop control unit controls the pressure to ensure that the estimated value of total oxygen delivery is above a predetermined threshold or within a predetermined range.

According to some embodiments of the present invention the apparatus further comprises an envelope elimination unit designed and configured for reducing or

eliminating amplitude modulation of the input radiofrequency signals so as to provide input radiofrequency signals of substantially constant envelope.

According to some embodiments of the present invention the apparatus further comprises: a mixer configured for mixing the output radiofrequency signals and the input radiofrequency signals, to provide a mixed radiofrequency signal; and a radiofrequency filter for filtering out a portion of the mixed radiofrequency signal so as to substantially increase a signal-to-noise ratio of a remaining portion of the mixed radiofrequency signal.

According to some embodiments of the present invention the apparatus further comprises a filtering unit configured for filtering the input signals using dynamically variable filter.

According to some embodiments of the present invention the cardiac output is calculated using a linear relationship between the phase shift and the cardiac output.

According to some embodiments of the present invention the dynamically variable filter is adapted in response to a change in a physiological condition of the subject.

According to some embodiments of the invention the physiological condition is a heart rate of the subject.

According to some embodiments of the invention a lower frequency bound characterizing the filter is about  $0.9*(HR/60)$  Hz at all times, wherein the HR is the heart rate in units of beats per minute.

According to some embodiments of the invention an upper frequency bound characterizing the filter is about  $6 + 1.5*[(HR/60) - 1]$  Hz at all times, wherein the HR is the heart rate in units of beats per minute.

Unless otherwise defined, all technical and/or scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments of the invention, exemplary methods and/or materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be necessarily limiting.

Implementation of the method and/or system of embodiments of the invention can involve performing or completing selected tasks manually, automatically, or a combination thereof. Moreover, according to actual instrumentation and equipment of embodiments of the method and/or system of the invention, several selected tasks 5 could be implemented by hardware, by software or by firmware or by a combination thereof using an operating system.

For example, hardware for performing selected tasks according to embodiments of the invention could be implemented as a chip or a circuit. As software, selected tasks according to embodiments of the invention could be 10 implemented as a plurality of software instructions being executed by a computer using any suitable operating system. In an exemplary embodiment of the invention, one or more tasks according to exemplary embodiments of method and/or system as described herein are performed by a data processor, such as a computing platform for executing a plurality of instructions. Optionally, the data processor includes a volatile 15 memory for storing instructions and/or data and/or a non-volatile storage, for example, a magnetic hard-disk and/or removable media, for storing instructions and/or data. Optionally, a network connection is provided as well. A display and/or a user input device such as a keyboard or mouse are optionally provided as well.

## 20 BRIEF DESCRIPTION OF THE DRAWINGS

Some embodiments of the invention are herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of embodiments of the invention. In this 25 regard, the description taken with the drawings makes apparent to those skilled in the art how embodiments of the invention may be practiced.

In the drawings:

FIG. 1 is a flowchart diagram of a method suitable for monitoring sleep of a sleeping subject according to various exemplary embodiments of the present 30 invention;

FIG. 2 shows cardiac output response of a female subject during positive end expiratory pressure treatment, as measured according to some embodiments of the present invention and further measured using a pulmonary artery catheter;

FIG. 3 is a flowchart diagram of a more detailed method suitable for monitoring sleep according to various exemplary embodiments of the present invention;

FIGs. 4a-b show a representative example of dynamically varying frequency bounds, employed according to embodiments of the present invention;

FIG. 4c show a representative example of a dynamically varying frequency band, employed according to embodiments of the present invention;

FIG. 5 is a schematic illustration of apparatus for monitoring sleep, according to various exemplary embodiments of the present invention;

FIG. 6 is a schematic illustration of a signal processing unit, according to various exemplary embodiments of the present invention;

FIG. 7 is a block diagram of electronic circuitry, according to various exemplary embodiments of the present invention; and

FIG. 8 is a schematic illustration of a system for monitoring sleep of a sleeping subject.

#### DESCRIPTION OF SPECIFIC EMBODIMENTS OF THE INVENTION

The present invention, in some embodiments thereof, relates to medical application and, more particularly, but not exclusively, to a method, apparatus and system for monitoring sleep.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not necessarily limited in its application to the details of construction and the arrangement of the components and/or methods set forth in the following description and/or illustrated in the drawings and/or the Examples. The invention is capable of other embodiments or of being practiced or carried out in various ways.

Computer programs implementing the method according to embodiments of the present invention can commonly be distributed to users on a distribution medium such as, but not limited to, a floppy disk, CD-ROM and flash memory cards. From the distribution medium, the computer programs can be copied to a hard disk or a similar intermediate storage medium. The computer programs can be run by loading the computer instructions either from their distribution medium or their intermediate storage medium into the execution memory of the computer, configuring the computer

to act in accordance with the method of this invention. All these operations are well-known to those skilled in the art of computer systems.

The method, apparatus and system of the present embodiments are particularly useful for the analysis of sleep. Yet, the use of the present embodiments in other situations, such as general anesthesia or the like, is not excluded from the scope of the present invention.

The method, apparatus and system of the present embodiments are suitable for identifying sleep apnea events caused by blockage or partial blockage of breathing passageways and/or by lack or reduced neural drive to the respiratory muscles.

10 The recurrent episodes of nocturnal asphyxia, cerebral hypoxia and arousal from sleep that characterize sleep apnea lead to a series of secondary physiologic events, which in turn give rise to various clinical complications.

Some manifestations are neuropsychiatric and behavioral disturbances that generally arise from the fragmentation of sleep and loss of slow-wave sleep induced by the recurrent arousal responses. Manifestations of neuropsychiatric and behavioral disturbances include excessive daytime sleepiness, intellectual impairment, memory loss, personality disturbances and impotence. Other manifestations are cardiorespiratory in nature and are thought to arise from the recurrent episodes of nocturnal asphyxia. Cardiorespiratory manifestations include bradycardia followed 20 by tachycardia, tachyarrhythmia.

Central sleep apnea may also lead to secondary physiological and clinical consequences. Central sleep apnea can be identified in a wide spectrum of individuals with medical, neurological and/or neuromuscular disorders associated with diurnal alveolar hypoventilation or periodic breathing. In less severe cases, central sleep 25 apnea events particularly occur at sleep onset and in REM sleep. In clinically significant central sleep apnea, events occur also in other sleep stages. Manifestations of central sleep apnea may include alveolar hypoventilation syndrome, daytime hypercapnia, hypoxemia, recurrent respiratory failure, polycythemia, pulmonary hypertension and right-sided heart failure.

30 Chronic sleep apnea may lead to various serious complications such as heart failure. The mechanism by which sleep apnea patients develop heart failure relates to build up of intrathoracic pressure. During an apnea event the pressure in the chest builds due to deposition of carbon dioxide in the lungs with no ventilation. The rising

carbon dioxide pressure increases thoracic pressure and reduces the venous return to the right heart resulting in a reduced or failure of left ventricular function. Increased left ventricular after load, recurrent nocturnal hypoxemia and elevated sympathoadrenal activity also contribute to the reduced left ventricular function.

5 It was found by the present inventors that apnea events can be identified by monitoring cardiac output. Specifically, since a reduced left ventricular filling is accompanied by a drop in cardiac output, an apnea event can be identified when the cardiac output is reduced.

10 Referring now to the drawings, Figure 1 is a flowchart diagram of a method suitable for monitoring sleep of a sleeping subject according to various exemplary embodiments of the present invention.

15 It is to be understood that, unless otherwise defined, the method steps described hereinbelow can be executed either contemporaneously or sequentially in many combinations or orders of execution. Specifically, the ordering of the flowcharts diagrams is not to be considered as limiting. For example, two or more method steps, appearing in the following description or in the flowchart diagrams in a particular order, can be executed in a different order (*e.g.*, a reverse order) or substantially contemporaneously. Additionally, several method steps described below are optional and may not be executed.

20 The method is particularly useful for monitoring sleep using output radiofrequency signals transmitted to the subject during sleep and input radiofrequency signals received from the subject during sleep.

25 The method begins at step 10 and continues to step 12 in which a phase shift of the input radiofrequency signals relative to the output radiofrequency signals is determined. The method continues to step 14 in which a cardiac output is calculated, based on the phase shift. The method continues to step 16 in which the cardiac output is used for identifying sleep apnea events.

The method ends at step 18.

30 Before providing a further detailed description of the method and apparatus for monitoring sleep, as delineated hereinabove and in accordance with some embodiments of the present invention, attention will be given to the advantages and potential applications offered thereby.

The present inventors conducted experiments in which cardiac output response to positive end expiratory pressure was evaluated. Without being bound to any theory, it is postulated that positive end expiratory pressure can be surrogate for sleep apnea because it creates positive thoracic pressure induced by mechanical ventilation 5 in anesthetized subjects in intensive care units. The pressure dynamics in positive end expiratory pressure are similar to those observed during an apnea episode.

Figure 2 shows cardiac output response of a female subject during positive end expiratory pressure treatment in intensive care unit. The cardiac output was measured using a conventional pulmonary artery catheter (Swan-Ganz catheter), as well as non-invasively using the phase shift of the input relative to output radiofrequency signals according to various embodiments of the present invention. Measurements performed according to the present embodiments are designated NICOM (Non-Invasive Cardiac Output Monitoring), and measurements performed using the pulmonary artery catheter are designated SWANG. Onsets of positive end expiratory pressure are 10 marked by dark rectangles. 15

As shown in Figure 2, significant drops in cardiac output are correlated with the onset of positive end expiratory pressure. Thus, apnea events can be identified when the level of cardiac output is reduced.

In various exemplary embodiments of the invention an apnea event is 20 identified when the cardiac output as calculated using the phase shift between the radiofrequency signals is reduced by at least 30 %, more preferably at least 40 %, more preferably at least 50 % over a time period of less than two minutes. In embodiments in which arterial oxygen saturation (SPO<sub>2</sub>) is monitored, a lower threshold of comprises reduction can be employed. For example, an apnea event can 25 be identified when the calculated cardiac output is reduced by at least 25 % and the value of SPO<sub>2</sub> is significantly decreased (say, by more than 40 %).

Traditionally, sleep apnea is diagnosed via PSG. The logistics and cost of 30 PSG, however significantly complicate the ability to diagnose the condition. The present embodiments provide a screening modality which can be used in small facilities and at home. The present embodiments allow fast screening of many subjects, by providing each subject with a system operable to execute selected steps of the method described herein. The present embodiments also allow screening out subjects for which sleep study is no required, thereby saving significant resources.

The present embodiments can also be employed by subjects who already been diagnosed with sleep apnea and for whom a CPAP device has been prescribed. Specifically, the present embodiments can be used as a supplement to a conventional treatment (*e.g.*, a CPAP device) so as to assess the efficacy of treatment. For 5 example, the present embodiments can be used for determining whether or not a sufficient amount of oxygen is delivered to vital organs such as the brain, heart and kidneys. It is recognized that even when a CPAP device pushes air to the lungs, oxygen delivery from the cardio-pulmonary system to vital tissues is not guaranteed. For example, a significant drop in cardiac output may result in insufficient oxygen 10 delivery even when the CPAP device increases the oxygen content in the blood. In this case, a system according to some embodiments of the present invention can signal the CPAP device to increase the positive airway pressure and/or generate a wakening signal sensible by the sleeping subject.

A more detailed method for monitoring sleep according to some embodiments 15 of the present invention is illustrated in the flowchart diagram of Figure 3.

The method begins at step 20 and optionally continues to step 22 in which output radiofrequency signals are transmitted to the subject during sleep, and step 24 in which input radiofrequency signals are received from the subject during sleep. The 20 output radiofrequency signals can be generated by a radiofrequency generator which generates a periodic high frequency current output in response to a periodic control input signal. The current output can be transmitted to the subject via an arrangement of electrodes for carrying current output from the radiofrequency generator as known in the art. The electrodes can be connected to locations of the body of the subject, *e.g.*, above and below the heart. Since the transmission and reception of signals is done 25 during sleep, the electrodes are optionally and preferably placed on the subject's back so as not to interfere with upper body motion.

Current, generated by the radiofrequency generator, flows across the thorax and causes a voltage drop due to the impedance of the body. The input radiofrequency signals are typically, but not obligatorily, relate to the hemodynamic reactance of an 30 organ of the subject.

As used herein, "hemodynamic reactance" refers to the imaginary part of the impedance. Techniques for extracting the imaginary part from the total impedance are known in the art. Typically, such extraction is performed at hardware level but the use

of algorithm at a software level is not excluded from the scope of the present invention.

According to some embodiments of the present invention the method continues to step 26 in which amplitude modulation of the input radiofrequency signals is reduced or, more preferably, eliminated. Optionally and preferably the phase modulation of the signals is maintained. The input radiofrequency signals typically carry a substantial amount of AM noise, which can be described, without limitation as a signal  $v(t)\cos(\omega t+\varphi(t))$ , which contains both phase and amplitude modulation. According to some embodiments the method generates signals having a substantial constant envelope, e.g.,  $v_0\cos(\omega t+\varphi(t))$ , where  $v_0$  is substantially a constant. The obtained signals thus represent the phase (or frequency) modulation of the input radiofrequency signal. The reduction or elimination of the amplitude modulation can be achieved, for example, using a limiter amplifier which amplifies the radiofrequency signals and limits their amplitude such that the amplitude modulation is removed.

In some embodiments, the method proceeds to step 28 in which the output radiofrequency signals are mixed with the input radiofrequency signals so as to provide a mixed radiofrequency signal. According to a preferred embodiment of the present invention, the mixed radiofrequency signal is composed of a plurality of radiofrequency signals, which may be, in one embodiment, a radiofrequency sum and a radiofrequency difference. A sum and a difference may be achieved, e.g., by multiplying the input and output signals. Since a multiplication between two frequencies is equivalent to a frequency sum and a frequency difference, the mix signal is composed of the desired radiofrequency sum and radiofrequency difference.

One ordinarily skilled in the art would appreciate that the advantage in the production of a radiofrequency sum and a radiofrequency difference is that whereas the radiofrequency sum includes both the signal and a considerable amount of electrical noise, the radiofrequency difference is approximately noise-free.

According to a preferred embodiment of the method continues to step 30 in which a portion of the mixed signal is filtered out such that a remaining portion of the mixed signal is characterized by a signal-to-noise ratio (SNR) which is substantially higher compared to the signal-to-noise ratio of the mixed signal or input radiofrequency signal.

The method continues to step 32 in which a phase shift  $\Delta\phi$  of the input radiofrequency signals relative to the output radiofrequency signals is determined. It was found by the inventors of the present invention that the phase shift of the input signals, as received from the subject, relative to the output signals as generated by the 5 radiofrequency generator, is indicative of the cardiac output of the subject.

The advantage of using  $\Delta\phi$  for determining the cardiac output is that the relation between the blood flow and  $\Delta\phi$  depends on fewer measurement-dependent quantities as compared to conventional determination techniques in which the impedance is used. The phase shift can be determined for any frequency component 10 of the spectrum of radiofrequency signals received from the organ. For example, in one embodiment, the phase shift is preferably determined from the base frequency component, in another embodiment the phase shift is preferably determined from the second frequency component, and so on. Alternatively the phase shift can be determined using several frequency components, *e.g.*, using an appropriate averaging 15 algorithm.

In some embodiments of the present invention the method continues to step 34 in which a dynamically variable filter is applied. The dynamically variable filter filters the data according to a frequency band which is dynamically adapted in response to a change in the physiological condition of the subject. It was found by the 20 Inventor of the present invention that the dynamical adaptation of the frequency band to the physiological condition of the subject can significantly reduce the influence of unrelated signals on the measured property.

Thus, in the present embodiment, step 34 includes a process in which first the 25 physiological condition of the subject is determined, then a frequency band is selected based on the physiological condition of the subject, and thereafter the input signals are filtered according to frequency band. The frequency band is dynamically adapted in response to a change in the physiological condition.

The physiological condition is preferably, but not obligatorily, the heart rate of the subject. The data pertaining to the physiological condition can be collected via a 30 suitable data collection unit either in analog or digital form, as desired. For example, the physiological condition can be a heart rate which can be determined, *e.g.*, by analysis of ECG signals or the like.

While the embodiments below are described with a particular emphasis to physiological condition which is a heart rate, it is to be understood that more detailed reference to the heart rate is not to be interpreted as limiting the scope of the invention in any way. For example, in exemplary embodiments of the present invention the 5 physiological condition is a ventilation rate of the subject, a repetition rate of a particular muscle unit and/or one or more characteristics of an action potential sensed electromyography.

The adaptation of the frequency band to the physiological condition can be according to any adaptation scheme known in the art. For example, one or more 10 parameters of the frequency band (*e.g.*, lower bound, upper bound, bandwidth, central frequency) can be a linear function of a parameter characterizing the physiological condition. Such parameter can be, for example, the number of heart beats per minute.

A representative example of a dynamically varying frequency bounds is illustrated in Figures 4a-b. Shown in Figures 4a-b is the functional dependence of the 15 frequency bounds (upper bound in Figure 4a and lower bound in Figure 4b) on the heart rate of the subject. As shown in Figure 4a, the upper bound of the frequency band varies linearly such that at a heart rate of about 60 beats per minute (bpm) the upper bound is about 6 Hz, and at a heart rate of about 180 bpm the upper bound is about 9 Hz. Preferably, the upper bound is about  $6 + 1.5 \times [(\text{HR}/60) - 1]$  Hz at all 20 times, where HR is the heart rate of the subject in units of bpm. As shown in Figure 4b, the lower bound of the frequency band varies linearly such that at a heart rate of about 60 the lower bound is about 0.9 Hz bpm and at a heart rate of about 180 bpm the lower bound is about 2.7 Hz. The lower bound is about  $0.9 \times (\text{HR}/60)$  Hz at all times.

As used herein the term “about” refers to  $\pm 10\%$ .

25 A dynamically varying band pass filter (BPF) characterized by the frequency bounds described above is illustrated in Figure 4c. As shown, each heart rate is associated with a frequency band defined by a lower bound and an upper bound. For example, for a heart rate of 60 bpm, Figure 4c depicts a BPF in which the lower bound is about 0.9 Hz and the upper bound is about 6 Hz.

30 It is to be understood that the values presented above and the functional relations illustrated in Figures 4a-b are exemplary embodiments and should not be considered as limiting the scope of the present invention in any way. In other exemplary embodiments, the functional relations between the frequency band and the

physiological condition can have different slopes and/or offsets, or they can be non-linear.

The method continues to step 36 in which the cardiac output is calculated, based on  $\Delta\varphi$ . It was found by the inventor of the present invention that there is a linear relationship between  $\Delta\varphi$  and the cardiac output, with a proportion coefficient comprising the systolic ejection time,  $T$ . For example, the cardiac output CO can be calculated using the relation  $CO = \text{const.} \times T \times \Delta\varphi \times HR$ , where HR is the heart rate of the subject (e.g., in units of beats per minutes), and "const." is a constant which can be found, for example, using a calibration curve.

10 In some embodiments of the present invention, the method continues to step 38 in which blood oxygen content is measured. This can be done, for example, using a conventional non-invasive pulse oximeter, which provides an approximation of the saturation of oxyhemoglobin ( $SpO_2$ ). Optionally, the method estimates or receives as input the hemoglobin concentration of the sleeping subject, and uses the hemoglobin 15 concentration to estimate blood oxygen content. The blood oxygen content can be supplemented to the calculated cardiac output for the purpose of improving sensitivity and/or specificity. In some embodiments of the present invention the method continues to step 40 in which the total oxygen delivery is estimated. The total oxygen delivery can be estimated by combining the cardiac output, oxyhemoglobin saturation 20 and hemoglobin concentration. For example, total oxygen delivery rate (typically expressed in units of mL of oxygen per minute) can be estimated by multiplying the cardiac output by the oxygen content.

In some embodiments of the present invention the method continues to step 42 in which positive airway pressure delivered to the subject is controlled, based on the 25 estimated value of the total oxygen delivery. In various exemplary embodiments of the invention the control of airway pressure is in a closed loop feedback with the estimation of total oxygen delivery. Thus, the method controls the delivered positive airway pressure such as to ensure that the estimated amount of total oxygen delivery rate is above a predetermined threshold, or within a predetermined range.

30 The method continues to step 44 in which the calculated cardiac output is used for identifying sleep apnea events. Generally, sleep apnea events correlate with a significantly fast drop in the cardiac output (see the non limiting example of Figure 2). Thus, according to the a preferred embodiment of the present invention, when the

cardiac output is reduced by a predetermined percentage over a sufficiently short and predetermined time period, the method identifies sleep apnea event. In various exemplary embodiments of the invention an apnea event is identified when the cardiac output is reduced by at least 30 %, more preferably at least 40 %, more preferably at 5 least 50 % over a time period of less than two minutes. Upon identification of an apnea event the method optionally generate a wakening signal (step 46).

When other quantities are measured and/or estimated, these quantities are optionally and preferably used together with the calculated cardiac output for identifying sleep apnea events. Addition of other quantities may aid in reducing false 10 positive and false negative identification solely based on cardiac output alone. For example, blood oxygen content can be supplemented to the cardiac output, wherein a sleep apnea event can be identified when there is a predetermined drop in cardiac output and a predetermined drop in oxygen content.

When the total oxygen delivery is estimated by the method, the estimated value 15 can be used to identify apnea event and/or to asses subject condition. For example, when the total oxygen delivery falls below a predetermined threshold which can be expressed as percentage of baselines, the method can generate a wakening alarm sensible by the sleeping subject or control a CPAP device to increase pressure.

The method ends at step 48.

Reference is now made to Figure 5 which is a schematic illustration of apparatus 400 for monitoring sleep of a sleeping subject 121, according to various 20 exemplary embodiments of the present invention.

Apparatus 400 comprises an input unit 142 for receiving input radiofrequency signals sensed from the organ. The input radiofrequency signals typically comprise 25 radiofrequency signals related to the electrical properties of the organ (e.g., bioimpedance which may generally relate to the impedance and/or hemodynamic reactance of the organ). The signals are sensed from one or more sensing locations 408 on the organ of subject 121 and are originated by output radiofrequency signals 124 generated by a radiofrequency generator 122.

Apparatus 400 further comprises a signal processing unit 404 which processes 30 the input radiofrequency signals. The processing may include, for example, mixing, demodulation, determination of phase shift, analog filtering, sampling and any combination thereof. Signal processing unit 404 may or may not be in communication

with radiofrequency generator 122, as desired. A representative example of signal processing unit 404 is provided hereinunder with reference to Figure 6.

Apparatus 400 is optionally and preferably designed for determining a phase shift  $\Delta\phi$  of signals 126 relative to signals 124. This can be done using a phase shift determinator 50 (not shown, see Figure 6) which can operate according to any known technique for determining a phase shift. The phase shift can be determined for any frequency component of the spectrum of radiofrequency signals received from the organ. For example, in one embodiment, the phase shift is determined from the base frequency component, in another embodiment the phase shift is determined from the second frequency component, and so on. Alternatively the phase shift can be determined using several frequency components, e.g., using an appropriate averaging algorithm.

The input radiofrequency signals may include one or more noise components, which may be introduced into the signal due to various reasons, e.g., subject agitation or breathing. In various exemplary embodiments of the invention apparatus 400 is capable of reducing or eliminating these noise components. In some embodiments of the present invention apparatus 400 further comprises a filtering unit 406 which filters the processed input signals. Unit 406 preferably performs the filtration operation in the frequency domain. Thus, in various exemplary embodiments of the invention, a series of samples of the processed radiofrequency signals are transformed, e.g., by a Fast Fourier Transform (FFT), to provide a spectral decomposition of the signals in the frequency domain. The transformation to the frequency domain can be done by a data processor. Algorithms for performing such transformations are known to those skilled in the art of signal processing.

The obtained spectral decomposition of the signal is filtered by unit 406 which typically eliminates one or more of the frequencies in the spectrum, depending on the upper and lower frequency bounds of the filter employed by unit 406. Unit 406 preferably employs a dynamically variable filter, such as, but not limited to, the dynamically variable filer described hereinabove.

In some embodiments of the present invention apparatus 400 comprises a cardiac output calculator 52 which calculates the cardiac output as further detailed hereinabove. Optionally, apparatus 400 comprises an estimator 54 which estimates total oxygen delivery as further detailed hereinabove. Estimator 54 can communicate

with a blood oxygen measuring device (not shown, see Figure 8) and receive oxygen data therefrom for the purpose of performing the estimations. Estimator 54 can also receive hemoglobin concentration as input and use the hemoglobin concentration in combination with data received from the blood oxygen measuring device to estimate 5 the oxygen content. For example, when the blood oxygen measuring device provides saturation data, such as arterial oxygen saturation, the oxygen content can be estimated as the product of arterial oxygen saturation, hemoglobin concentration and a constant, which reflects the hemoglobin-oxygen binding capacity.

A sleep apnea identification unit 56 uses the calculated cardiac output and 10 identifies sleep apnea events as further detailed hereinabove. In embodiments in which estimator 54 is employed unit 56 optionally and preferable uses the estimated quantity (oxygen content, total oxygen delivery) in combination with the calculated cardiac output for identifying sleep apnea events. Unit 56 can also be configured to receive oxygen content data from a blood oxygen measuring device or from estimator 15 54 and use the oxygen content data in combination with the calculated cardiac output for identifying sleep apnea events. Calculator 52 and estimator 54 can be associated with a data processor 142. Data processor 142 can also be employed by unit 406 for performing the transformation to the frequency domain and/or eliminating the frequency components according to the dynamically variable frequency bounds.

20 Data processor 142 can also be configured for calculating other quantities, *e.g.*, stroke volume and/or other blood-volume related quantities.

Optionally, apparatus 400 comprises a closed-loop control unit 144 which receives the estimated value of total oxygen delivery from estimator 54 and controls 25 pressure delivered by a respiratory therapy device (not shown, see Figure 8) based on the estimated value. In various exemplary embodiments of the invention closed-loop control unit 144 controls the pressure to ensure that the estimated value of total oxygen delivery is above a predetermined threshold or within a predetermined range.

Reference is now made to Figure 6 which schematically illustrates signal processing unit 404, according to various exemplary embodiments of the present 30 invention. Unit 404 preferably comprises a mixer 128, electrically communicating with generator 122, for mixing output signals 124 and input signals 126, so as to provide a mixed radiofrequency signal. Signals 124 and 126 may be inputted into

mixer 128 through more than one channel, depending on optional analog processing procedures (e.g., amplification) which may be performed prior to the mixing.

Mixer 128 may be any known radiofrequency mixer, such as, but not limited to, double-balanced radiofrequency mixer and unbalanced radiofrequency mixer.

5 According to a preferred embodiment of the present invention, the mixed radiofrequency signal is composed of a plurality of radiofrequency signals, which may be, in one embodiment, a radiofrequency sum and a radiofrequency difference. A sum and a difference may be achieved, e.g., by selecting mixer 128 such that signals 124 and signals 126 are multiplied thereby. Since a multiplication between two 10 frequencies is equivalent to a frequency sum and a frequency difference, mixer 128 outputs a signal which is composed of the desired radiofrequency sum and radiofrequency difference.

According to various exemplary embodiments of the present invention unit 404 further comprises a phase shift determinator 50 for determining the phase shift of the 15 input signals relative to the output signal. Phase shift determinator 50 can determine the phase shift according to any technique known in the art. For example, the phase shift can be determined from the radiofrequency difference outputted from mixer 128.

According to a preferred embodiment of the present invention processing unit 404 further comprises electronic circuitry 132, which filters out a portion of the signal 20 such that a remaining portion of the signal is characterized by a substantially increased signal-to-noise ratio.

Circuitry 132 is better illustrated in Figure 7. According to an embodiment of the present invention circuitry 132 comprises a low pass filter 134 to filter out the high 25 frequency content of the signal. Low pass filter 134 is particularly useful in the embodiment in which mixer 128 outputs a sum and a difference, in which case low pass filter 134 filters out the radiofrequency sum and leaves the approximately noise-free radiofrequency difference. Low pass filter 134 may be designed and constructed in accordance with the radiofrequency difference of a particular system which employs apparatus 400. A judicious design of filter 134 substantially reduces the noise content 30 of the remaining portion.

Circuitry 132 preferably comprises an analog amplification circuit 136 for amplifying the remaining portion of the signal. The construction and design of analog amplification circuit 136 is not limited, provided circuit 136 is capable of amplifying

the signal. Amplification circuits suitable for the present embodiments are found in International Patent Application, Publication Nos. WO 2004/098376 and WO 2006/087696 the contents of which are hereby incorporated by reference.

According to a preferred embodiment of the present invention circuitry **132** further comprises a digitizer **138** for digitizing the signal. The digitization of the signal is useful for further digital processing of the digitized signal, *e.g.*, by a microprocessor.

Optionally, circuitry comprises a differentiator **140** (either a digital differentiator or an analog differentiator) for performing at least one time-differentiation of the measured impedance to obtain a respective derivative (*e.g.*, a first derivative, a second derivative, *etc.*) of the bioimpedance or hemodynamic reactance. Differentiator **140** may comprise any known electronic functionality (*e.g.*, a chip) that is capable of performing analog or digital differentiation.

According to a preferred embodiment of the present invention signal processing unit **404** comprises an envelope elimination unit **135** which reduces or, more preferably, eliminates amplitude modulation of signals **126**. Optionally and preferably, unit **135** maintains the phase modulation of signals **126**. The output of unit **135** represents the phase (or frequency) modulation of signal **126**, as further detailed hereinabove. Unit **135** can employ, for example, a limiter amplifier which amplifies signals **126** and limits their amplitude such that the amplitude modulation is removed. The advantage of the removal of the amplitude modulation is that it allows a better determination of the phase shift  $\Delta\varphi$  between the input and output signals, as further detailed hereinabove.

Reference is now made to Figure 8, which is a schematic illustration of system **120** for monitoring sleep of a subject, according to a preferred embodiment of the present invention. System **120** preferably comprises a radiofrequency generator **122**, for generating output radiofrequency signals. Generator **122** may be embodied as any radiofrequency generator. System **120** further comprises a plurality of electrodes **125**, which are connected to the skin of subject **121**. Electrodes **125** transmit output radiofrequency signals **124**, generated by generator **122** and sense input radiofrequency signals **126** originated from the organ of subject **121**.

System **120** preferably comprises any of the components of apparatus **400** described above. According to a preferred embodiment of the present invention

system 120 further comprises a detector 129 for detecting a voltage drop on a portion of the body of subject 121 defined by the positions of electrodes 125. In response to the detected voltage, detector 129 preferably generates signals which are indicative of impedance of the respective portion of the body. In this embodiment, the stroke 5 volume can be calculated using  $(dX/dt)_{max}$ , as further detailed hereinabove. Knowing the stroke volume, the cardiac output is calculated by multiplying the stroke volume by the heart rate of the subject. More preferably, detector 129 generates signals which are indicative of a hemodynamic reactance,  $X$ .

In some embodiments, system 120 comprises a blood oxygen measuring 10 device 150 which provides apparatus 400 with oxygen data via a communication line 152. Device 150 can be, for example, a conventional pulse oximeter or the like. Apparatus 400 combines the calculated cardiac output with the oxygen content data for identifying sleep apnea as further detailed hereinabove. The system In some 15 embodiments of the present invention can comprise a display for displaying status of sleep (e.g., continually showing cardiac output and/or total oxygen delivery). The system can also comprise an alarm device for generating a wakening signal. The alarm preferably communicates with apparatus 400 which signals the alarm to generate the awakening signal upon occurrence of a sleep apnea event or when the total oxygen delivery is below a predetermined threshold.

System 120 can also comprise a respiratory therapy device 154, such as, but 20 not limited to, a continuous positive airway pressure (CPAP) device. Device 154 can comprise a blower connected through a hose and a mask, such as a nasal mask or a nasal cannula, to the patient's respiratory airway. Device 54 can also include an air flow sensor and an air pressure sensor. Device 154 can be controlled by apparatus 400 25 (e.g., via the closed-loop control unit 144, see Figure 5) so as to ensure that the estimated oxygen delivery rate is above a predetermined threshold or within a predetermined range. Thus, a closed loop feedback can be established so as to continuously monitor the oxygen delivery as estimated by apparatus 400 and the pressure of air flow delivered by device 154, and to vary the pressure to accord with 30 the estimated oxygen delivery.

Following are technical preferred values which may be used for selective steps and parts of the embodiments described above.

The output radiofrequency signals are preferably from about 10 KHz to about 200 KHz in frequency and from about 10mV to about 200mV in magnitude; the input radiofrequency signals are preferably about 75 KHz in frequency and about 20mV in magnitude; a typical impedance which can be measured by the present embodiments is 5 from about 5 Ohms to about 75 Ohms; the resulting signal-to-noise ratio of the present embodiments is at least 40dB; low pass filter 134 is preferably characterized by a cutoff frequency of about 35Hz and digitizer 138 preferably samples the signals at a rate of about 500-1000 samples per second.

10 The terms "comprises", "comprising", "includes", "including", "having" and their conjugates mean "including but not limited to".

The term "consisting of means "including and limited to".

15 The term "consisting essentially of" means that the composition, method or structure may include additional ingredients, steps and/or parts, but only if the additional ingredients, steps and/or parts do not materially alter the basic and novel characteristics of the claimed composition, method or structure.

As used herein, the singular form "a", "an" and "the" include plural references unless the context clearly dictates otherwise. For example, the term "a compound" or "at least one compound" may include a plurality of compounds, including mixtures thereof.

20 Throughout this application, various embodiments of this invention may be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a 25 range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

30 Whenever a numerical range is indicated herein, it is meant to include any cited numeral (fractional or integral) within the indicated range. The phrases "ranging/ranges between" a first indicate number and a second indicate number and "ranging/ranges from" a first indicate number "to" a second indicate number are used

herein interchangeably and are meant to include the first and second indicated numbers and all the fractional and integral numerals therebetween.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination or as suitable in any other described embodiment of the invention. Certain features described in the context of various embodiments are not to be considered essential features of those embodiments, unless the embodiment is inoperative without those elements.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims.

All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention. To the extent that section headings are used, they should not be construed as necessarily limiting.

## WHAT IS CLAIMED IS:

1. A method of monitoring sleep of a sleeping subject using output radiofrequency signals transmitted to the subject during sleep and input radiofrequency signals received from the subject during sleep, the method comprising:
  - determining a phase shift of the input radiofrequency signals relative to the output radiofrequency signals;
  - calculating cardiac output based on said phase shift; and
  - using said cardiac output for identifying sleep apnea events.
2. The method of claim 1, further comprising supplementing said cardiac output with blood oxygen content, wherein said identification of said sleep apnea events is based on said cardiac output and said blood oxygen content.
3. A method of monitoring sleep of a sleeping subject, comprising:
  - transmitting output radiofrequency signals to the subject during sleep;
  - receiving input radiofrequency signals from the subject during sleep; and
  - executing the method of claim 1.
4. The method of claim 3, further comprising measuring blood oxygen content and supplementing said cardiac output with blood oxygen content, wherein said identification of said sleep apnea events is based on said cardiac output and said blood oxygen content.
5. The method of claim 1 or 3, further comprising inputting or estimating hemoglobin concentration of the sleeping subject, wherein said identification of said sleep apnea events is based on said cardiac output and said hemoglobin concentration.
6. The method of claim 5, further comprising estimating total oxygen delivery and generating a wakening signal when an estimated value is below a predetermined threshold.

7. The method of claim 6, wherein said identification of said sleep apnea events is further based on said estimated value of said total oxygen delivery.

8. The method of claim 6, further comprising controlling positive airway pressure delivered to the sleeping subject based on said estimated value.

9. The method of claim 1 or 3, further comprising reducing or eliminating amplitude modulation of said input radiofrequency signals so as to provide input radiofrequency signals of substantially constant envelope.

10. The method of claim 1 or 3, further comprising mixing said output radiofrequency signals and said input radiofrequency signals so as to provide a mixed radiofrequency signal, and filtering out a portion of said mixed radiofrequency signal so as to substantially increase a signal-to-noise ratio of a remaining portion of said mixed radiofrequency signal.

11. The method of claim 1 or 2, further comprising applying a dynamically variable filter.

12. Apparatus for monitoring sleep of a sleeping subject using output radiofrequency signals transmitted to the subject during sleep and input radiofrequency signals received from the subject during sleep, the apparatus comprising:

a phase shift determinator configured for determining a phase shift of the input radiofrequency signals relative to the output radiofrequency signals;

a cardiac output calculator configured for calculating cardiac output based on said phase shift; and

a sleep apnea identification unit configured for identifying sleep apnea events based on said cardiac output.

13. A system for monitoring sleep of a sleeping subject, comprising:

a radiofrequency generator for generating output radiofrequency signals;

a plurality of electrodes designed for transmitting said output radiofrequency signals to the subject and for sensing input radiofrequency signals from the subject; and

the apparatus of claim 12.

14. The system of claim 13, further comprising a blood oxygen measuring device.

15. The apparatus or system of claim 13, wherein the apparatus further comprises a total oxygen delivery estimator configured for estimating total oxygen delivery.

16. The apparatus or system of claim 15, wherein said sleep apnea identification unit is configured to identify said sleep apnea events based on an estimated value of said total oxygen delivery and said cardiac output.

17. The apparatus or system of claim 13, wherein the apparatus further comprises a closed-loop control unit configured for receiving estimated value of said total oxygen delivery and controlling pressure delivered by a respiratory therapy device based on said estimated value.

18. The system of claim 17, further comprising said respiratory therapy device.

19. The apparatus or system of claim 12 or 13, wherein the apparatus further comprises an envelope elimination unit designed and configured for reducing or eliminating amplitude modulation of said input radiofrequency signals so as to provide input radiofrequency signals of substantially constant envelope.

20. The apparatus or system of claim 12 or 13, wherein the apparatus further comprises:

a mixer configured for mixing said output radiofrequency signals and said input radiofrequency signals, to provide a mixed radiofrequency signal; and

a radiofrequency filter for filtering out a portion of said mixed radiofrequency signal so as to substantially increase a signal-to-noise ratio of a remaining portion of said mixed radiofrequency signal.

21. The apparatus or system of claim 12 or 13, wherein the apparatus further comprises a filtering unit configured for filtering said input signals using dynamically variable filter.

22. The method, apparatus or system of claim 1, 3, 12 or 13, wherein said cardiac output is calculated using a linear relationship between said phase shift and said cardiac output.

23. The method, apparatus or system of claim 11 or 21, wherein said dynamically variable filter is adapted in response to a change in a physiological condition of the subject.

24. The method, apparatus or system of claim 23, wherein said physiological condition is a heart rate of the subject.

25. The method, apparatus or system of claim 24, wherein a lower frequency bound characterizing said filter is about  $0.9*(HR/60)$  Hz at all times, wherein said HR is said heart rate in units of beats per minute.

26. The method, apparatus or system of claim 24, wherein an upper frequency bound characterizing said filter is about  $6 + 1.5*[(HR/60) - 1]$  Hz at all times, wherein said HR is said heart rate in units of beats per minute.

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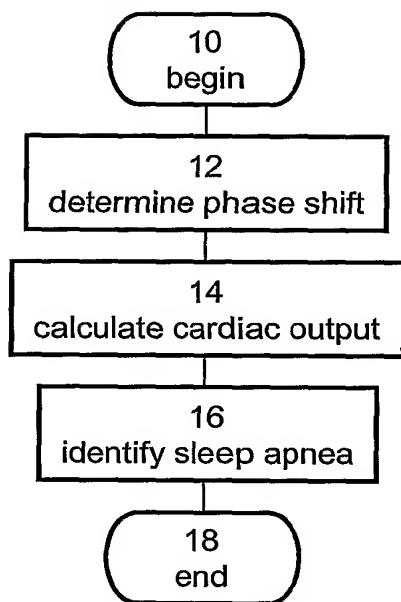


Fig. 1

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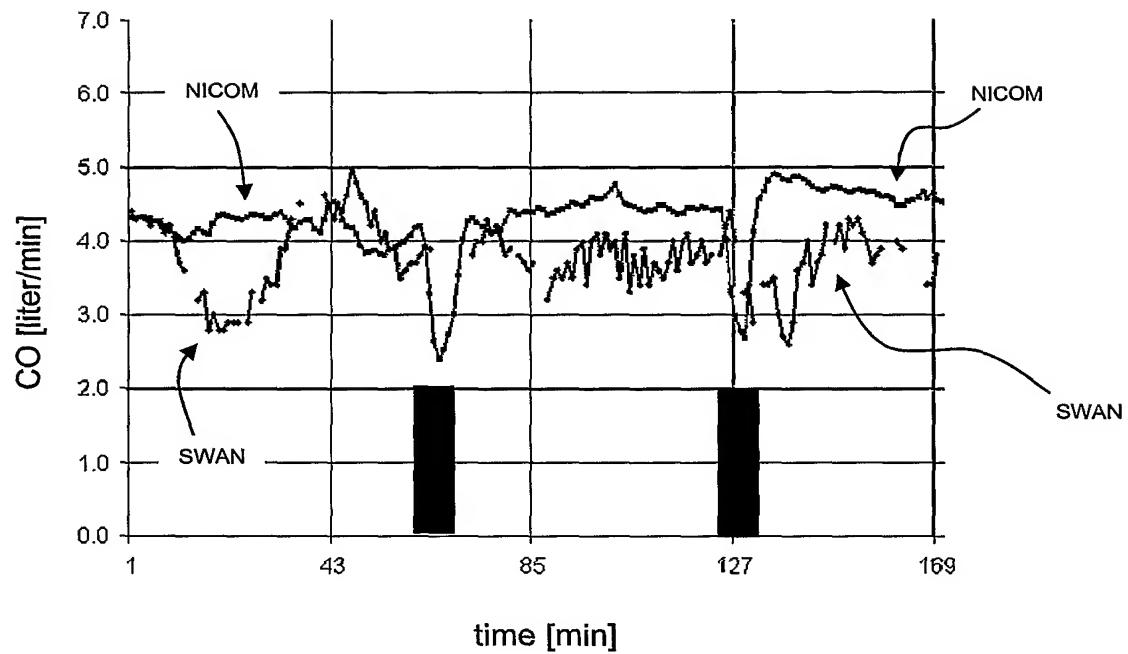


Fig. 2

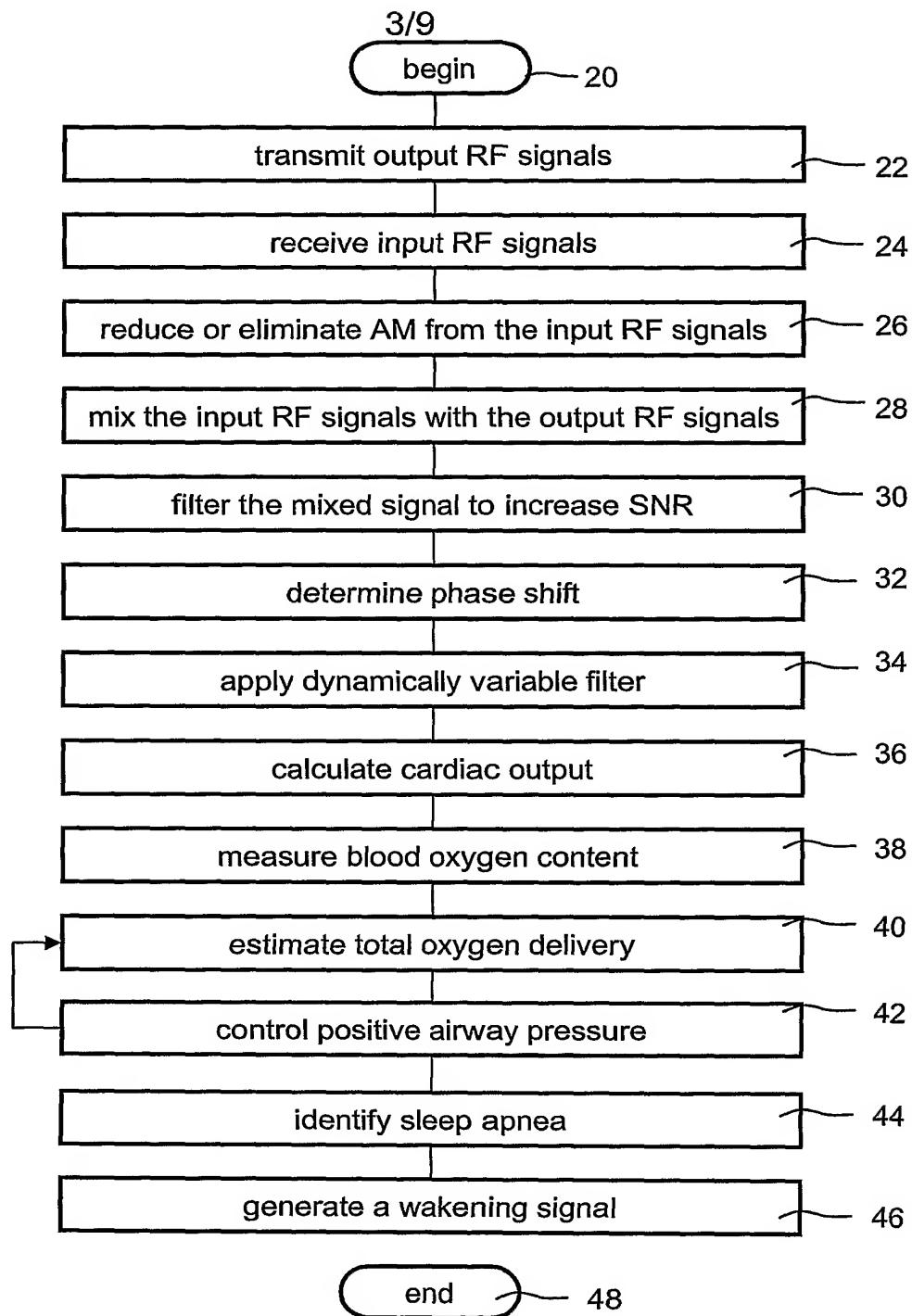


Fig. 3

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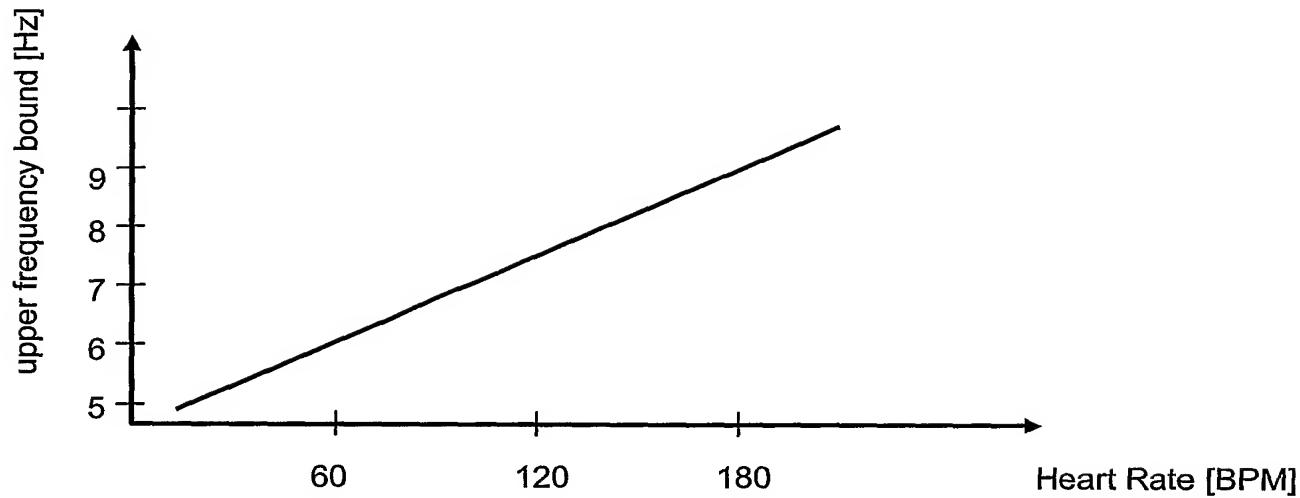


Fig. 4a

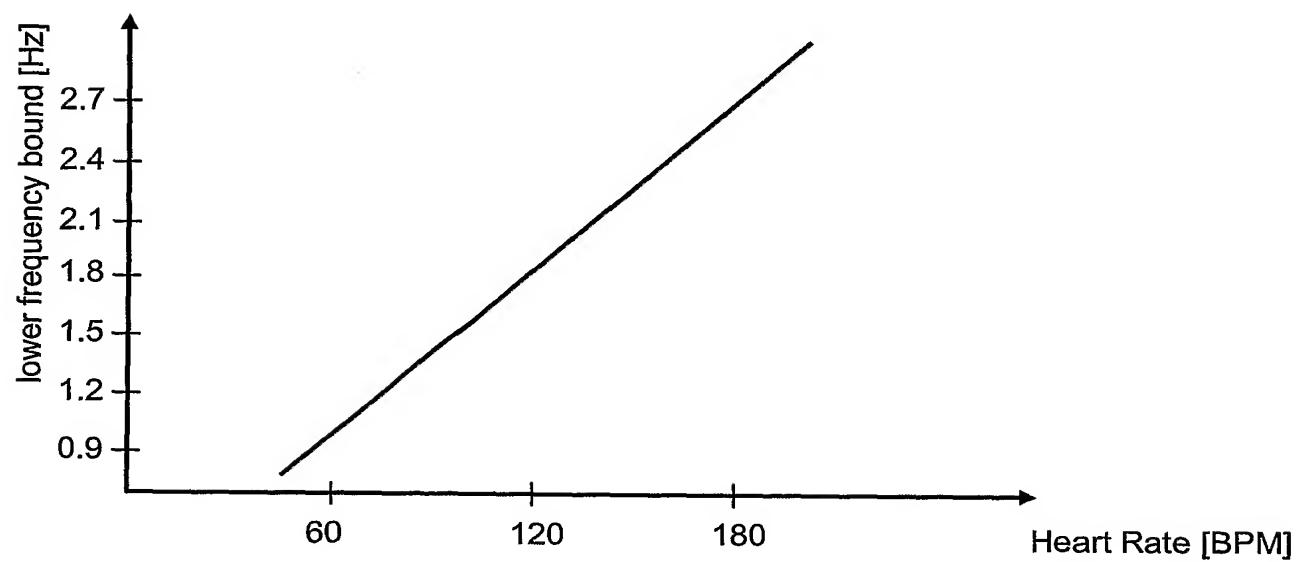


Fig. 4b

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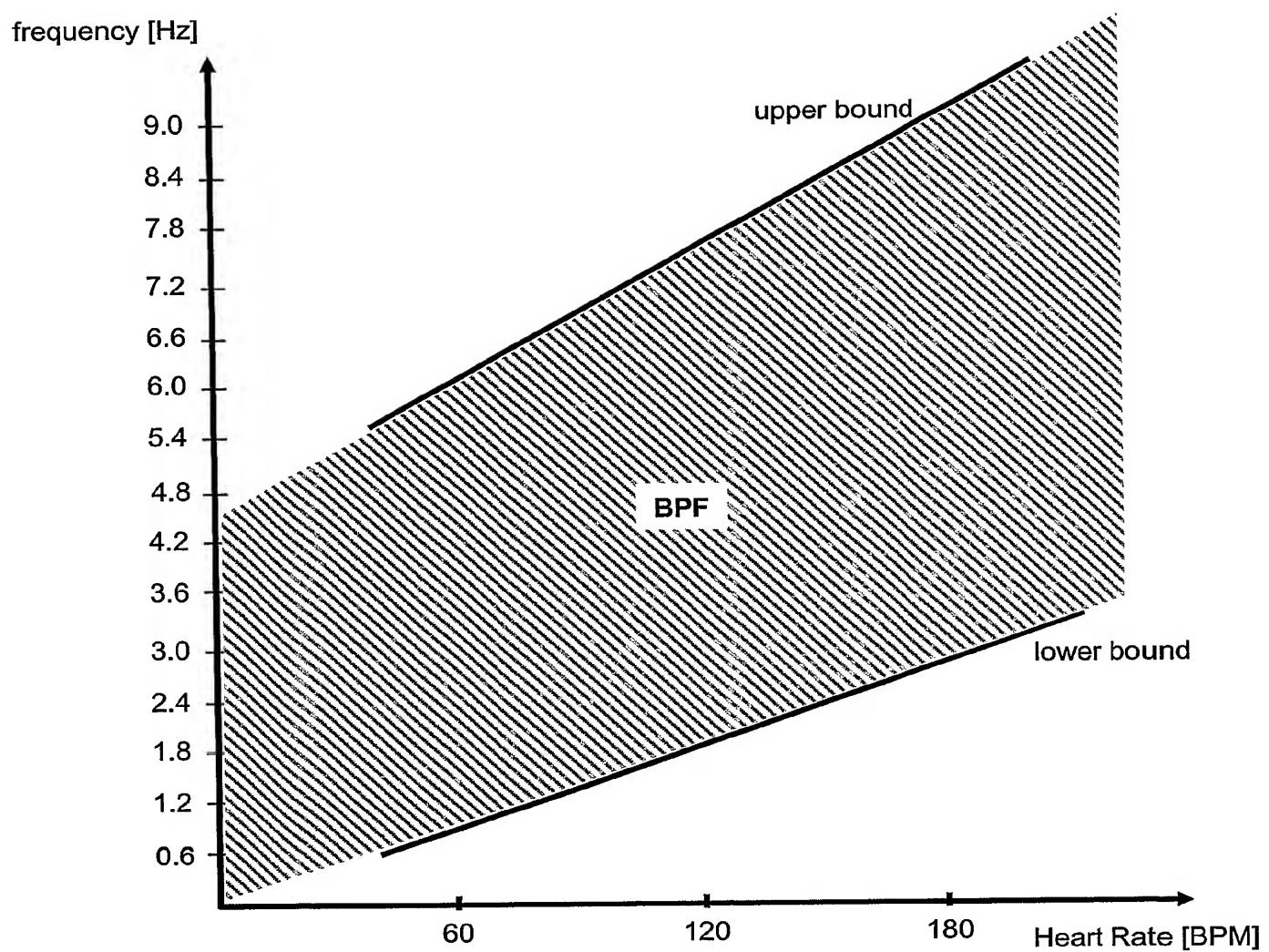


Fig. 4c

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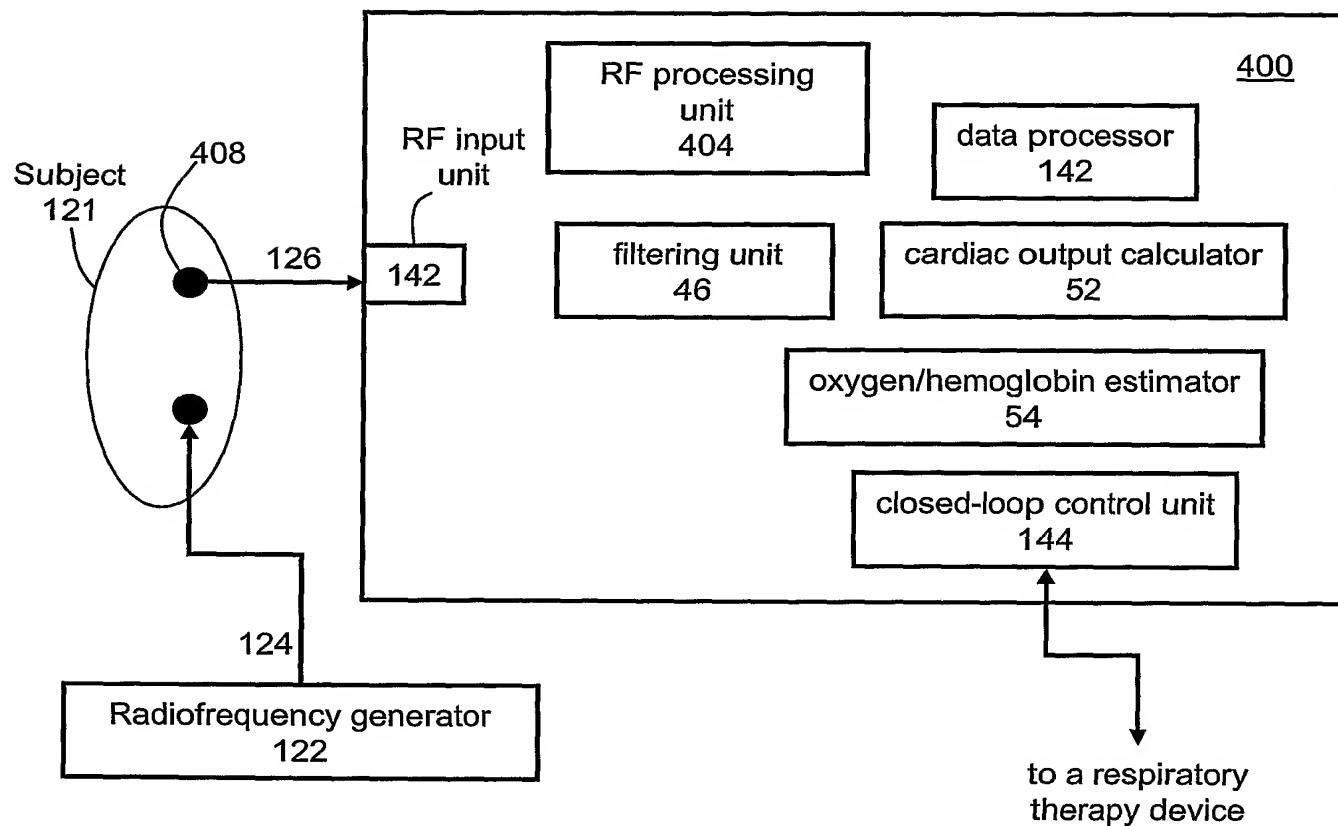


Fig. 5

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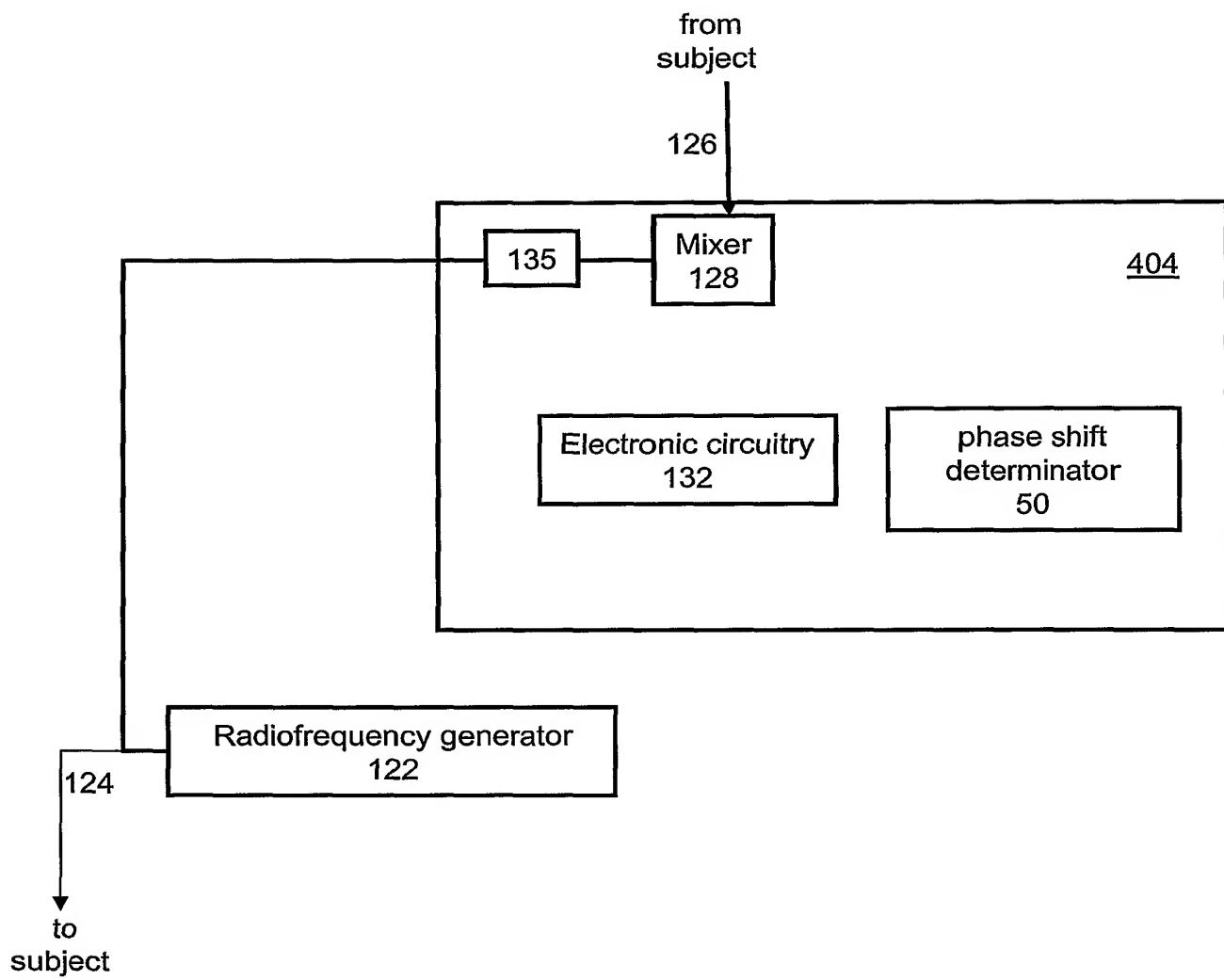


Fig. 6

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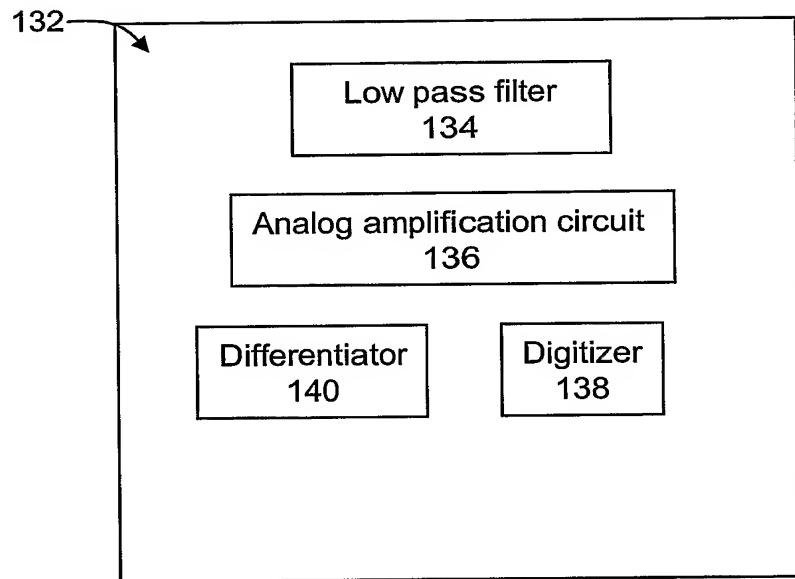


Fig. 7

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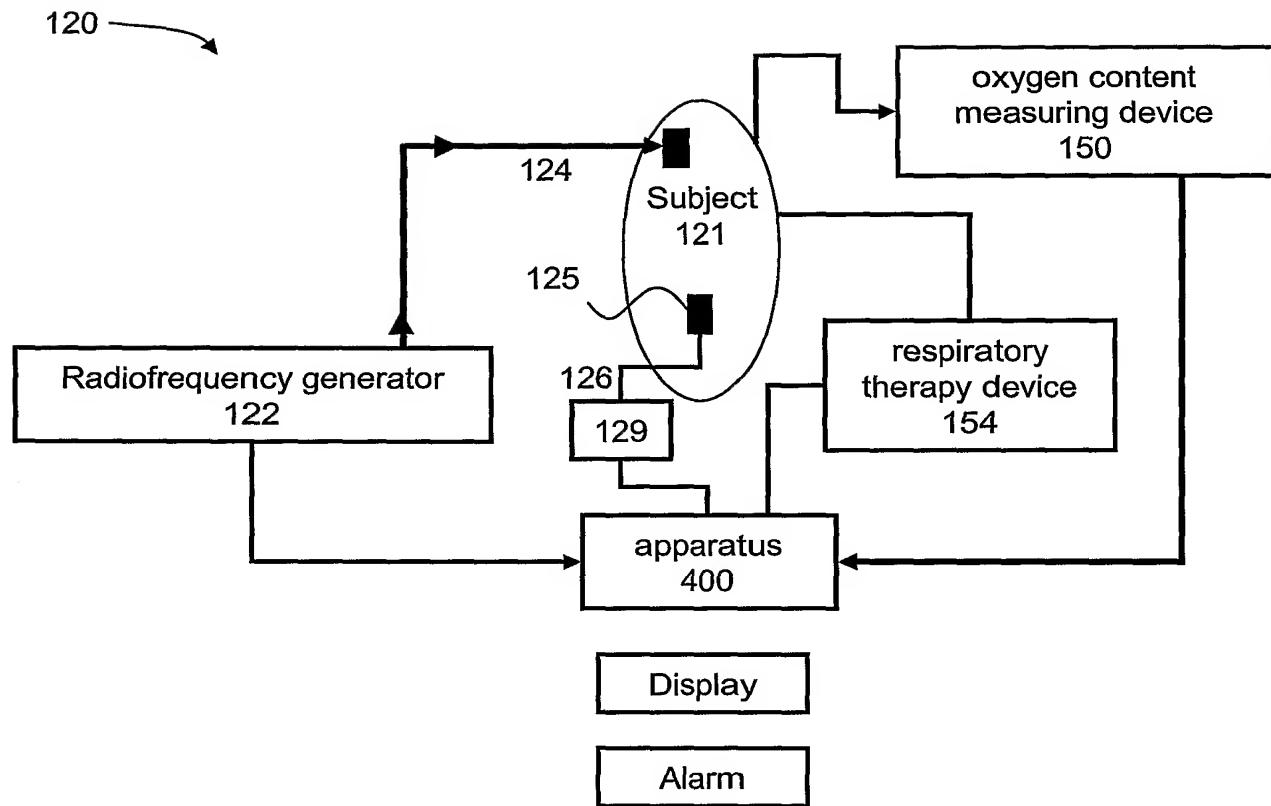


Fig. 8

# INTERNATIONAL SEARCH REPORT

International application No

PCT/IL2008/000309

**A. CLASSIFICATION OF SUBJECT MATTER**  
 INV. A61B5/053 A61B5/029  
 ADD. A61B5/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
**A61B A61M**

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**EPO-Internal, WPI Data, BIOSIS, EMBASE**

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
|-----------|---|-----------------------|
| Y         | <p>DATABASE BIOSIS [Online]<br/>         BIOSCIENCES INFORMATION SERVICE,<br/>         PHILADELPHIA, PA, US; 1992,<br/>         STOOHS R ET AL: "CARDIOVASCULAR CHANGES<br/>         ASSOCIATED WITH OBSTRUCTIVE SLEEP APNEA<br/>         SYNDROME"<br/>         XP002488467<br/>         Database accession no. PREV199293105800<br/>         abstract<br/>         &amp; STOOHS R ET AL: "CARDIOVASCULAR CHANGES<br/>         ASSOCIATED WITH OBSTRUCTIVE SLEEP APNEA<br/>         SYNDROME" JOURNAL OF APPLIED PHYSIOLOGY,<br/>         vol. 72, no. 2, 1992, pages 583-589,<br/>         ISSN: 8750-7587</p> <p style="text-align: center;">-/-</p> | 12-26                 |

Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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| Date of the actual completion of the international search  | Date of mailing of the international search report |
| 17 July 2008   | 05/08/2008   |
| Name and mailing address of the ISA/<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl<br>Fax: (+31-70) 340-3016 | Authorized officer<br><br><b>Görlich, Tobias</b>   |

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/IL2008/000309

| C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT |  |  |
|--|--|--|
| Category*  | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No.                        |
| Y  | WO 2006/087696 A (NEW LEAF CAPITAL LTD [GB]; KEREN HANAN [IL]; SIMON AVRAM B [GB]) 24 August 2006 (2006-08-24)<br>cited in the application<br>page 19, line 22 – page 23, line 29<br>page 30, line 17 – page 31, line 12<br>figures 2-9<br>-----<br>RAZA S B ET AL: "FILTERING RESPIRATION AND LOW-FREQUENCY MOVEMENT ARTEFACTS FROM THE CARDIOGENIC ELECTRICAL IMPEDANCE SIGNAL"<br>MEDICAL AND BIOLOGICAL ENGINEERING AND COMPUTING, SPRINGER, HEIDELBERG, DE,<br>vol. 30, no. 5,<br>1 September 1992 (1992-09-01), pages<br>556-561, XP000323425<br>ISSN: 0140-0118<br>the whole document<br>-----<br>DATABASE EMBASE [Online]<br>ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM,<br>NL; May 1994 (1994-05),<br>SCHUMACKER P T ET AL: "Oxygen delivery and uptake relationships in patients with aortic stenosis"<br>XP002488468<br>Database accession no. EMB-1994152503<br>abstract<br>& SCHUMACKER P T ET AL: "Oxygen delivery and uptake relationships in patients with aortic stenosis" AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE 199405 US,<br>vol. 149, no. 5, May 1994 (1994-05), pages<br>1123-1131,<br>ISSN: 1073-449X<br>-----<br>US 2005/217674 A1 (BURTON DAVID [AU] ET AL) 6 October 2005 (2005-10-06)<br>paragraphs [0053], [0054]<br>figure 1<br>-----<br>WO 2004/112606 A (UNIV COLLEGE DUBLIN NAT UNIVER [IE]; KAPNISAKIS IOANIS [GR]; HENEGHAN) 29 December 2004 (2004-12-29).<br>page 3, line 4 – page 9, line 12<br>figure 8<br>----- | 12-26<br>19-26<br>15,16<br>17,18<br>12,13,21 |
|  |  | -/-  |

## INTERNATIONAL SEARCH REPORT

International application No

PCT/IL2008/000309

## C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
|-----------|--|-----------------------|
| A         | BAKSHI M S ET AL: "Circulatory response in sleep apnea patients during sleep before and after CPAP treatment"<br>SLEEP (ROCHESTER), vol. 28, no. Suppl. S, 2005, page A194, XP008094214<br>& 19TH ANNUAL MEETING OF THE ASSOCIATED-PROFESSIONAL-SLEEP-SOCIETIES; DENVER, CO, USA; JUNE 18 -23, 2005<br>ISSN: 0161-8105<br>abstract   | 12, 13,<br>17, 18     |
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## INTERNATIONAL SEARCH REPORT

International application No

PCT/IL2008/000309

## C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IL2008/000309

## Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: 1-11 because they relate to subject matter not required to be searched by this Authority, namely:  
**Article 17(2)(a)(i) and Rule 39.1(iv) PCT – Diagnostic method**
2.  Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International application No

PCT/IL2008/000309

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